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Role of potassium channels in the modulation of insulin release

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In this issue of *Diabetologia*, Pickkers et al. have put forward an interesting hypothesis on the cellular mechanism of action of thiazide-induced hyperglycaemia. In the past few years, these investigators have documented convincingly that the vasorelaxing properties of thiazide diuretics can be explained by opening of calcium-activated potassium (K_{Ca}) channels in vascular smooth muscle cells. Since these particular potassium channels also occur in pancreatic beta cells, they reason that thiazides are expected to hyperpolarize the pancreatic beta cell with subsequent closure of the voltage-dependent calcium channel. This mechanism could explain the fall in intracellular calcium and, as a consequence, reduction in insulin release as previously reported by Sandström [1].

The hypothesis of Pickkers et al. is primarily based on in vitro observations of the effects of thiazides on vascular smooth muscle cells. Actually, they extrapolate findings on the acute effects of thiazide diuretics on vascular smooth muscle cells in vitro to the chronic exposure of pancreatic cells to thiazides in vivo. Of course, this must be interpreted with caution because there are no data to show that the hyperpolarizing response to thiazides persists during long-term exposure. In this regard it is also interesting to realize that the acute and direct vasodilator properties of thiazides could not be reproduced in an in vivo setting in humans [2]. Moreover, the K_{Ca} channels of the smooth muscle cells and of pancreatic beta cells may belong to the same family, but this does not exclude important tissue differences in channel characteristics. For the so-called ATP-dependent potassium

(K_{ATP}) channels these tissue differences are well-known. The K_{ATP} channel opener and experimental vasodilator drug levcromakalim for example is highly effective at the level of the smooth muscle cells, but is hardly able to open pancreatic K_{ATP} channels [3]. As a consequence, this experimental drug will not result in inhibition of insulin secretion at therapeutic concentrations, whereas these concentrations will give rise to a potent vasodilator response. Apparently, this experimental drug can be classified as a vascular selective K_{ATP} channel opener. It is important to realize that in the hypothesis of Pickkers et al., the authors assume that thiazide diuretics will act as non-selective K_{Ca} openers.

A rise in intracellular calcium concentration is the final common pathway in the stimulus-secretion coupling of insulin in pancreatic beta cells [4]. Apart from uptake and release from intracellular calcium stores, intracellular calcium concentration is dependent on the influx of calcium through voltage operated calcium channels. The key role of calcium in the exocytosis of insulin-containing secretory granules is emphasized in experiments with calcium entry blockers. In the isolated rat pancreas, insulin release was inhibited by verapamil [5], a potent calcium entry blocker known to inhibit excitation-contraction coupling in both myocardial and vascular smooth muscle cells. Insulin secretion was also found to be slightly reduced in patients with required treatment with the dihydropyridine derivative nifedipine [6]. However, in clinical practice the diabetogenic effect of calcium entry blockers appears to be small [7].

The open state probability of voltage operated calcium channels is also highly dependent on the membrane potential. Since the membrane potential is mainly regulated by the opening and closure of potassium channels, insulin secretion of the beta cell may be significantly modulated by substances interfering with pancreatic potassium channels. As such, the

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Abbreviations: K_{Ca} , Calcium-activated potassium channel; K_{ATP} , ATP-dependent potassium channel; CGRP, calcitonin gene related peptide; IAPP, islet amyloid polypeptide.

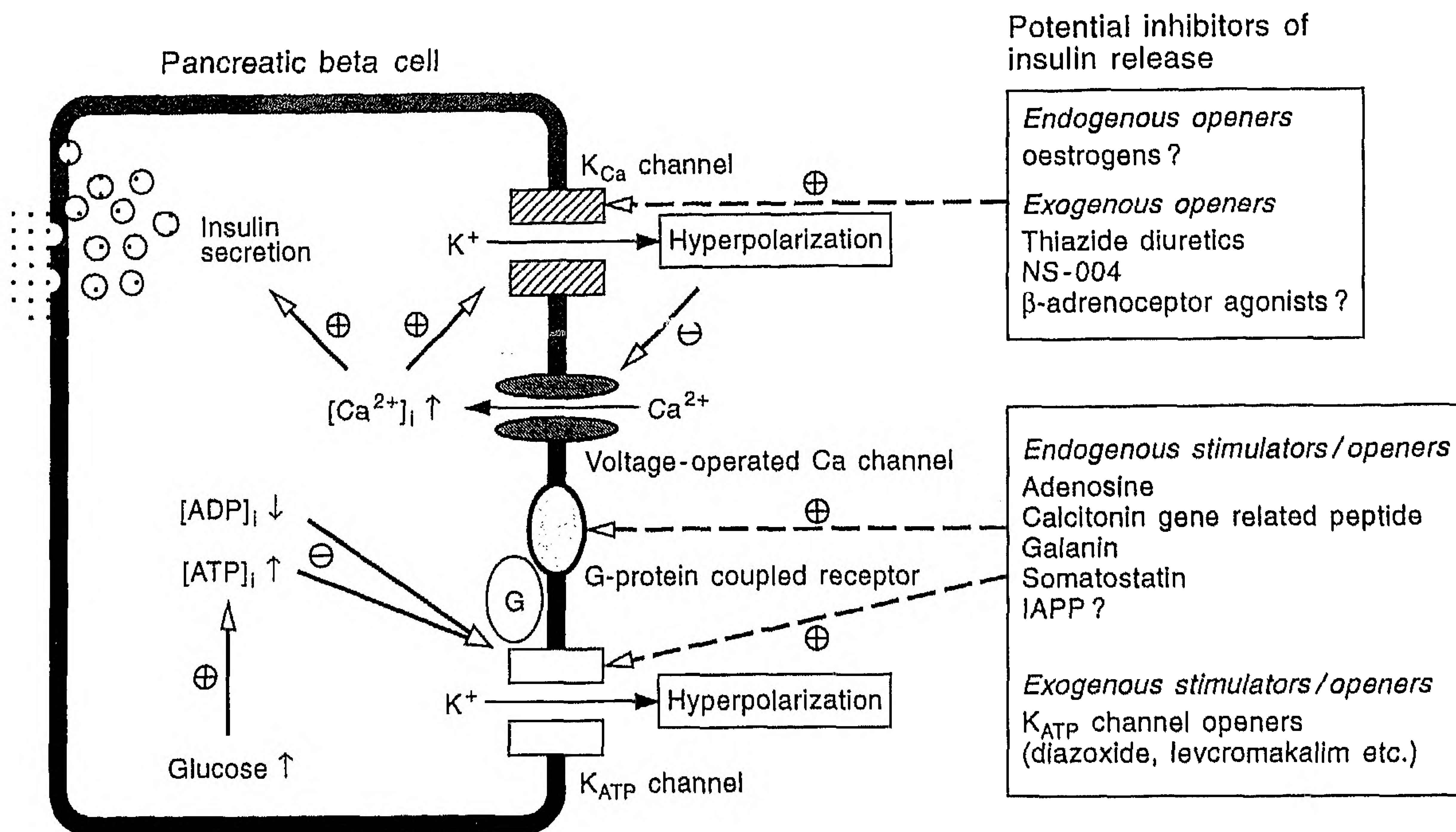


Fig. 1. Schematic representation of the pancreatic beta cell. Outline of potential effects of endogenous and exogenous substances that open ATP-dependent (K_{ATP}) or calcium-activated (K_{Ca}) potassium channels. Opening of potassium channels results in potassium efflux, and subsequent hyperpolarization. This hyperpolarization closes voltage operated calcium channels, thereby reducing intracellular calcium ($[Ca^{2+}]_i$) and

related insulin release. Some of the agents are assumed to bind directly to the potassium channel (for example the diabetogenic drug diazoxide), whereas others are thought to act via stimulation of specific receptors coupled to the channel (for example adenosine via the A_1 adenosine receptor). \oplus Positive stimulation; in case of channels this is similar to opening; \ominus Inhibition; in case of channels, this is similar to closing

mechanisms of action of thiazide diuretics suggested by Pickkers et al. may be relevant to all kinds of substances which interact with potassium channels and or alter membrane potential. Apart from a variety of drugs, several endogenous substances can also interfere with pancreatic potassium channels. Figure 1 is a schematic representation of the effect of potassium channel opening on the pancreatic beta cell.

A striking example of an endogenous potassium channel opener is somatostatin. Somatostatin is a well-known and potent inhibitor of insulin secretion, and is used for this purpose in humans as a tool to block insulin secretion in experimental conditions and to treat insulinoma-associated hypoglycaemia. This peptide has been shown to hyperpolarize the membrane by opening of K_{ATP} channels [8], and therefore illustrates the importance of the control of membrane potential in pancreatic insulin release. Similar mechanisms may be relevant to galanin and calcitonin gene related peptide (CGRP). Indeed, CGRP is a potent vasodilator substance in several organ systems, including the human skeletal muscle vascular bed [9]. Experiments with the sulphonylurea derivative glibenclamide, a well-known blocker of K_{ATP} channels, have shown that CGRP exerts its effects at least in part by opening of K_{ATP} channels [10]. Direct infusion of CGRP into the pancreatic artery is able to inhibit glucose-induced insulin release

by almost 50% [11]. Up to now, the cellular mode of action of this CGRP-effect is not clear, but the putative interaction with pancreatic potassium channels warrants further attention. Interestingly, the chemical structure of CGRP shows striking similarity with that of islet amylin polypeptide (IAPP). In patients with non-insulin-dependent diabetes mellitus IAPP concentrations are increased and are reported to contribute to the impaired secretion of insulin [12]. In this regard it is tempting to speculate that the cellular mechanism of action of the IAPP-induced reduction in insulin release is based on opening of K_{ATP} channels in the pancreatic beta cells. As such, sulphonylurea derivatives may be expected to be more potent in patients with high IAPP concentrations in the pancreas. The polypeptide galanin is also able to hyperpolarize cell membranes by opening of K_{ATP} channel. Both in vivo and in the isolated perfused pancreas, galanin abolished insulin secretion [13–15].

In contrast to the extensive knowledge on the modulation of K_{ATP} channels, data on the effects of endogenous or pharmacological agents on the open probability of K_{Ca} channels are scarce. Recently, White et al. [16] observed that oestrogens are able to open K_{Ca} channels in smooth muscle cells. In their in vitro preparation, oestradiol showed a vasorelaxant effect which was inhibited by the highly selective K_{Ca} channel blocker charybdotoxin. In line with the

hypothesis of Pickkers et al. this potassium channel opening property of oestrogens may offer a cellular mechanism to explain the observed direct inhibiting effect of this sex hormone on pancreatic insulin release [17]. Up to now, there appear to be no pharmacological agents which selectively interact with K_{Ca} channels. For this reason, the observation that thiazide diuretics open this channel in smooth muscle cells and possibly also in the pancreatic beta cells make this class of drugs of special interest.

From these data it is obvious that modulation of the open probability of potassium channels at the level of the pancreatic beta cells is of major importance with respect to insulin secretion. It has to be emphasized that the diabetogenic mechanism of action of a wide variety of substances has not been elucidated. Therefore, all drugs or endogenous hormones that affect glucose metabolism should be investigated on their ability to interact with potassium channels. Because of the availability of highly selective blockers of the various potassium channels, these investigations are relatively easy to perform in an in vitro preparation. The patch clamp technique even enables these kinds of investigations at a cellular or single channel level. It will be much more complicated to determine whether these proposed mechanisms of action are also of significance in the in vivo situation.

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